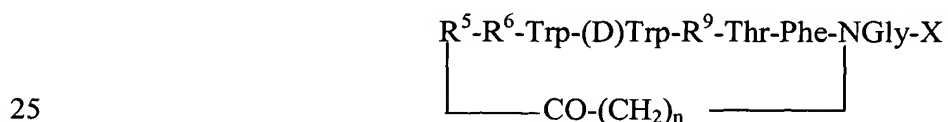


## THE CLAIMS

What is claimed is:

1. A backbone cyclized analog of somatostatin of three to twenty-four amino acids that  
 5 incorporates at least one building unit, said building unit containing one nitrogen atom  
 of the peptide backbone connected to a bridging group comprising an amide, thioether,  
 thioester, disulfide, urea, carbamate, or sulfonamide, wherein at least one building unit  
 is connected via the bridging group to form a cyclic structure with a moiety selected  
 from the group consisting of a second building unit, the side chain of an amino acid  
 10 residue of the sequence or a terminal amino acid residue, further comprising a  
 chelating moiety covalently bound to said backbone cyclized analog.
2. The backbone cyclized analog of claim 1 wherein the chelating moiety is selected from  
 a moiety comprising four donor atoms or eight donor atoms.
- 15 3. The somatostatin analog of claim 4 wherein the chelating moiety is selected from  
 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and  
 diethylenetriaminepentaacetic acid (DTPA).
- 20 4. The somatostatin analog of claim 1 wherein the backbone cyclized somatostatin analog  
 having the general Formula No. 6



Formula No. 6

wherein n is 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

30 R<sup>5</sup> is 1,3-dicarbonyl-cyclopropane, phthalic acid, maleic acid, glutamic acid,  
 valeric acid, diaminoethane-CO, diaminopropane-CO, or GABA;

R<sup>6</sup> is Phe or Tyr; and

R<sup>9</sup> is (L)- or (D)- Lys.

5. The backbone cyclized analog of claim 4 selected from the group of:

1,3-dicarbonyl-Cyclopropane\*-Tyr-Trp-(D)Trp-Lys-Thr-Phe-GlyN<sub>3</sub>-NH<sub>2</sub>;

Glutamic acid\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyN<sub>3</sub>-NH<sub>2</sub>;

Diaminoethane\*-CO-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC<sub>3</sub>-NH<sub>2</sub>;

5 Diaminoethane\*-CO-Tyr-Trp-(D)Trp-Lys-Thr-Phe-GlyC<sub>3</sub>-NH<sub>2</sub>;

Diaminopropan\*-CO-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC<sub>3</sub>-NH<sub>2</sub>;

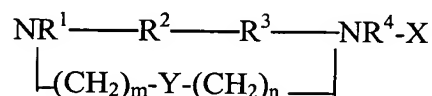
Diaminoethane\*-CO-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC<sub>3</sub>-NH<sub>2</sub>;

GABA\*-Phe-Trp-(D)Trp-(D)Lys-Thr-Phe-GlyC<sub>3</sub>-NH<sub>2</sub>;

GABA\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC<sub>3</sub>-NH<sub>2</sub>;

10 wherein the asterisk denotes that the bridging group is connected between the free functional group of that residue and the N<sup>α</sup>-ω-functionalized derivative of the Gly residue.

6. The somatostatin analog of claim 1 wherein the backbone cyclized somatostatin analog having the general Formula No. 7



20 Formula No. 7

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R<sub>1</sub> is Trp, (L)- or (D)- Lys, Ala, or Phe;

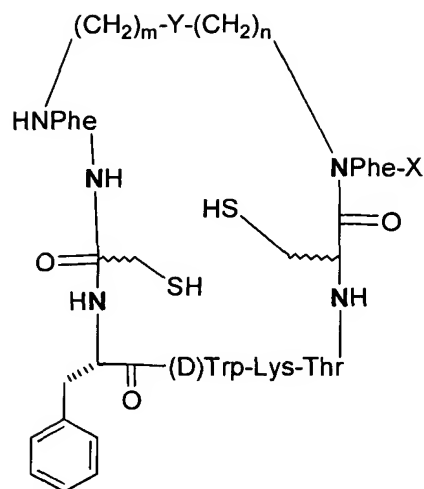
R<sub>2</sub> is Ala, (L)- or (D)- Trp, or Lys

25 R<sub>3</sub> is (D)Trp, (L)- or (D)- Phe, Lys, Pro, or (D)Ala;

R<sub>4</sub> is Lys, (D)Phe, (L)- or (D)- Ala, Trp, Gly; and

Y is amide, thioether, thioester, disulfide, urea, carbamate, or sulfonamide.

7. The somatostatin analog of claim 1 wherein the backbone cyclized somatostatin analog having the general Formula No. 8



Formula No. 8

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

- 5 Y is amide, thioether, thioester disulfide, urea, carbamate, or sulfonamide; and the two cysteine residues are independently L or D.

8. The somatostatin analog of claim 1 having the general Formula No. 5:

10 Z-Q-PTR

Formula No. 5

wherein

- 15 Z is a chelating moiety comprising: (i) four donor atoms selected from the group of  $N_3S$  and  $N_2S_2$  that through metal complexation form three five- to six-membered rings or (ii) eight donor atoms that, through metal complexation, form stable five- to six-membered rings;

Q is a direct bond or a linker moiety which can be coupled to a free functional group of the peptide; and PTR denotes a backbone cyclized SST analog according to the present invention.

20

9. The somatostatin analog of claim 8 wherein Q is selected from the group of a direct bond, diaminopropionic acid (Dpr), diaminobutyric acid (Dab), gamma aminobutyric

acid (GABA), aminohexanoic acid, polyethylene glycol (PEG), 4-aminobutyric acid, 6-aminocaproic acid, and  $\beta$ -alanine, and Z is selected from the group of mercaptoacetyl-Gly-Gly-Gly (MAG3), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA).

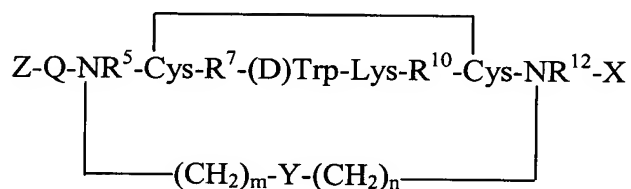
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10. The somatostatin analog of claim 9 wherein Z is selected from the group of mercaptoacetyl-Gly-Gly-Gly (MAG3), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA); and Q is selected from a direct bond and Gly.

10

11. The somatostatin analog of claim 8 wherein the backbone cyclized somatostatin analog having the general Formula No. 9

15



Formula No. 9

20

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

Q is a direct bond or a linker moiety which can be coupled to any free functional group of the peptide;

25

Z is a chelating moiety comprising: (i) four donor atoms selected from the group of  $\text{N}_3\text{S}$  and  $\text{N}_2\text{S}_2$  that through metal complexation form 5- to 6-membered rings or (ii) eight donor atoms that, through metal complexation, form stable five- to six-membered rings;

$\text{R}^5$  is (D)- or (L)-Phe or (D)- or (L)-Ala;

$\text{R}^7$  is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)-1Nal, or (D)- or (L)-2Nal, or (D)- or (L)-Tyr;

30

$\text{R}^{10}$  is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L)-Ala, or (D)- or (L)-Phe;

$\text{R}^{12}$  is (D)- or (L)-Phe or (D)- or (L)-Ala; and



Q is a direct bond or a linker moiety which can be coupled to a free functional group of the peptide;

R<sup>5</sup> is diaminobutyric acid or diaminopropionic acid;

R<sup>6</sup> is (D)- or (L)-Phe or Tyr;

5 R<sup>7</sup> is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)- 1Nal or (D)- or (L)- 2Nal, or Tyr;

R<sup>8</sup> is (D)- or (L)-Trp;

R<sup>9</sup> is (D)- or (L)-Lys;

R<sup>10</sup> is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L) -Ala, or (D)- or (L)- Phe;

10 R<sup>11</sup> is (D)- or (L)- Phe, (D)- or (L)- Ala, Nle, or Cys; and

R<sup>12</sup> is Gly, Val, Leu, (D)- or (L)-Phe or 1Nal or 2Nal.

14. The somatostatin analog of claim 13 wherein:

X is amide;

15 Q is selected from the group of a direct bond, Gly,  $\beta$ -Ala and GABA;

Z is DOTA or DTPA;

R<sup>5</sup> is diaminobutyric acid (Dab);

R<sup>6</sup> is Phe;

R<sup>7</sup> is Trp;

20 R<sup>8</sup> is (D)Trp;

R<sup>9</sup> is Lys;

R<sup>10</sup> is Thr;

R<sup>11</sup> is Phe;

R<sup>12</sup> is Gly; and

25 n is 3.

15. The somatostatin analog of claim 13 wherein the backbone cyclized somatostatin analog is selected from the group of:

In-DTPA-Gly-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

30 In-DTPA-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*- NH<sub>2</sub>;

In-DTPA- $\beta$ -Ala-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

In-DTPA-GABA-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

In-DTPA-5-aminopentanoic acid-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;  
In-DTPA-3-aminomethylbenzoic acid-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Dpr(MA)-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

5 ReO-MA-Dpr(MA)-Gly-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Dpr(MA)-βAla-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Dpr(MA)-GABA-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Dpr(MA)-5-aminopentanoic acid-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

10 ReO-MA-Dpr(MA)-6-aminohexanoic acid-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Gly-Gly-Gly-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Gly-Gly-Gly-Gly-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Gly-Gly-Gly-GABA-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

15 ReO-MA-Gly-Gly-Gly-5-aminopentanoic acid-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

wherein MA denotes mercaptoacetyl, Dpr denotes diaminopropionic acid, Dab denotes diaminobutyric acid, GABA denotes gamma aminobutyric acid, and the asterisk denotes that the bridging group is connected between the free functional group of that residue and the N<sup>α</sup>-ω-functionalized derivative of the Gly residue.

16. The backbone cyclized analog of claim 1 wherein the chelating moiety further comprises a complex with a radioisotope.

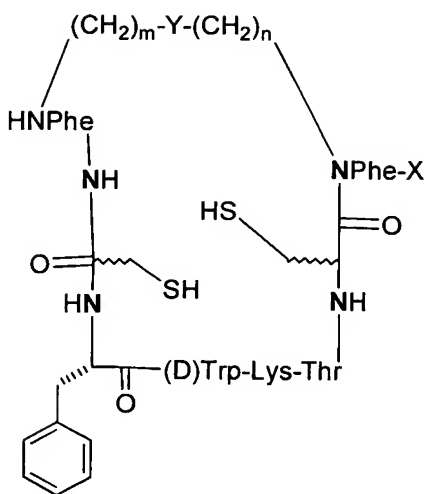
25 17. The somatostatin analog according to claim 16 wherein the radioisotope is selected from the group consisting of <sup>99m</sup>Tc, <sup>186</sup>Re, <sup>188</sup>Re, indium, yttrium, lutetium, gallium and gadolinium.

30 18. A method for diagnosing or treating cancer and allograft rejection comprising administration of a backbone cyclized analog of somatostatin of three to twenty-four amino acids that incorporates at least one building unit, said building unit containing one nitrogen atom of the peptide backbone connected to a bridging group comprising









Formula No. 8

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

5 Y is amide, thioether, thioester disulfide, urea, carbamate, or sulfonamide; and  
the two cysteine residues are independently L or D.

26. The method according to claim 18 having the general Formula No. 5:

10 Z-Q-PTR

Formula No. 5

wherein

Z is a chelating moiety comprising: (i) four donor atoms selected from the group of  $N_3S$  and  $N_2S_2$  that through metal complexation form three five- to six-membered rings  
15 or (ii) eight donor atoms that, through metal complexation, form stable five- to six-membered rings;

Q is a direct bond or a linker moiety which can be coupled to a free functional group of the peptide; and PTR denotes a backbone cyclized SST analog according to the present invention.

20

27. The method according to claim 26 wherein Q is selected from the group of a direct bond, diaminopropionic acid (Dpr), diaminobutyric acid (Dab), gamma aminobutyric

acid (GABA), aminohexanoic acid, polyethylene glycol (PEG), 4-aminobutyric acid, 6-aminocaproic acid, and  $\beta$ -alanine, and Z is selected from the group of mercaptoacetyl-Gly-Gly-Gly (MAG3), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA).

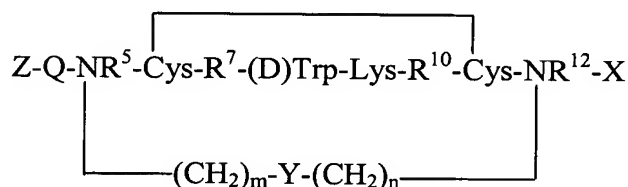
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28. The method according to claim 27 wherein Z is selected from the group of mercaptoacetyl-Gly-Gly-Gly (MAG3), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA); and Q is selected from a direct bond or Gly.

10

29. The method according to claim 26 wherein the backbone cyclized somatostatin analog having the general Formula No. 9

15



Formula No. 9

20

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

Q is a direct bond or a linker moiety which can be coupled to any free functional group of the peptide;

25

Z is a chelating moiety comprising: (i) four donor atoms selected from the group of  $\text{N}_3\text{S}$  and  $\text{N}_2\text{S}_2$  that through metal complexation form 5- to 6-membered rings or (ii) eight donor atoms that, through metal complexation, form stable five- to six-membered rings;

$\text{R}^5$  is (D)- or (L)-Phe or (D)- or (L)-Ala;

$\text{R}^7$  is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)-1Nal, or (D)- or (L)-2Nal, or (D)- or (L)-Tyr;

30

$\text{R}^{10}$  is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L)-Ala, or (D)- or (L)-Phe;

$\text{R}^{12}$  is (D)- or (L)-Phe or (D)- or (L)-Ala; and



R<sup>5</sup> is diaminobutyric acid or diaminopropionic acid.

R<sup>6</sup> is (D)- or (L)-Phe or Tyr;

R<sup>7</sup> is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)- 1Nal or (D)- or (L)- 2Nal, or Tyr;

5 R<sup>8</sup> is (D)- or (L)-Trp;

R<sup>9</sup> is (D)- or (L)-Lys;

R<sup>10</sup> is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L) -Ala, or (D)- or (L)- Phe;

R<sup>11</sup> is (D)- or (L)- Phe, (D)- or (L)- Ala, Nle, or Cys; and

R<sup>12</sup> is Gly, Val, Leu, (D)- or (L)-Phe or 1Nal or 2Nal.

10

32. The method according to claim 31 wherein:

X is amide;

Q is selected from the group of a direct bond, Gly,  $\beta$ -Ala and GABA;

Z is DOTA or DTPA;

15 R<sup>5</sup> is diaminobutyric acid (Dab);

R<sup>6</sup> is Phe;

R<sup>7</sup> is Trp;

R<sup>8</sup> is (D)Trp;

R<sup>9</sup> is Lys;

20 R<sup>10</sup> is Thr;

R<sup>11</sup> is Phe;

R<sup>12</sup> is Gly; and

n is 3.

25 33. The method according to claim 31 wherein the backbone cyclized somatostatin analog is selected from the group of:

In-DTPA-Gly-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

In-DTPA-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*- NH<sub>2</sub>;

In-DTPA- $\beta$ -Ala-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

30 In-DTPA-GABA-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

In-DTPA-5-aminopentanoic acid-Dab\*-Phe-Trp- (D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

In-DTPA-3-aminomethylbenzoic acid-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Dpr(MA)-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Dpr(MA)-Gly-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

5 ReO-MA-Dpr(MA)-βAla-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Dpr(MA)-GABA-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Dpr(MA)-5-aminopentanoic acid-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

10 ReO-MA-Dpr(MA)-6-aminohexanoic acid-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Gly-Gly-Gly-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Gly-Gly-Gly-Gly-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

ReO-MA-Gly-Gly-Gly-GABA-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

15 ReO-MA-Gly-Gly-Gly-5-aminopentanoic acid-Dab\*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3\*-NH<sub>2</sub>;

wherein MA denotes mercaptoacetyl, Dpr denotes diaminopropionic acid, Dab denotes diaminobutyric acid, GABA denotes gamma aminobutyric acid, DTPA denotes diethylenetriaminepentaacetic acid, and the asterisk denotes that the bridging group is connected between the free functional group of that residue and the N<sup>α</sup>-ω-functionalized derivative of the Gly residue.

34. The method according to claim 18 wherein the chelating moiety further comprises a complex with a radioisotope.

25 35. The method according to claim 34 wherein the radioisotope is selected from the group consisting of <sup>99m</sup>Tc, <sup>186</sup>Re, <sup>188</sup>Re, indium, yttrium, lutetium, gallium and gadolinium.

36. The method according to claim 18 wherein the backbone cyclic analog is selective for at least one somatostatin receptor subtype.

30

37. A method for diagnosing, treating or preventing of disorders selected from the group consisting of cancers, autoimmune diseases, endocrine disorders, diabetes-associated

5 complications, gastrointestinal disorders, inflammatory diseases, pancreatitis, atherosclerosis, restenosis, allograft rejection, and post-surgical pain, comprising administering to a mammal in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a backbone cyclized somatostatin analog according to claim 1.

38. The method according to claim 37 wherein the backbone cyclic analog is selective for at least one somatostatin receptor subtype.

10 39. A kit for preparing a scintigraphic imaging agent for imaging sites within a mammalian body, said kit comprising a backbone cyclized analog of somatostatin and a chelating moiety covalently bound to said backbone cyclized analog.

15